TRANSMEMBRANE AROMATIC AMINO ACID DISTRIBUTION IN P-GLYCOPROTEIN: IMPLICATIONS FOR BROAD SPECIFICITY.

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Multidrug resistance (MDR) in cancer cells is often associated with overexpression of P-glycoprotein (Pgp), a membrane protein believed to function as an ATP-dependent efflux pump which decreases the cellular accumulation of structurally diverse anticancer drugs (Endicott & Ling, 1989). A large number of compounds belonging to several classes, which include calcium channel blockers, antipsychotic drugs, anesthetics, steroids and detergents (Ford & Hait, 1990) are capable of reversing MDR. What confers on Pgp the capacity to recognize structurally unrelated compounds is not fully understood. Both cytotoxic drugs and modulating agents are lipophilic molecules with planer aromatic rings and a charged amino group at physiological pH. It has been suggested that drugs approach binding sites through the membrane-lipid bilayer (Higgins & Gottesman, 1992). We describe here the primary sequence analysis of the trans-membrane (TM) region of Pgp in combination with the molecular modelling technique which suggests that array of aromatic residues in the TM region of Pgp provides a well defined pocket for drug occupancy. Export mediated resistance to various antibiotics and disinfectants is a common occurrence in bacteria. The bacterial multidrug resistance protein (Bmr) in *B.Subtilis* (Neyfakh et al., 1991) and qacA in *S.aureus* (Tennent et al., 1989) efflux a number of known substrates of Pgp. There is some overlap of substrates and inhibitors between Pgp and neurotransmitter transporters (Giros & Caron, 1993). These two sets of proteins are also included in the analysis.
Based on a comparative primary sequence analysis of Pgp and related proteins, in conjunction with available data regarding modulator structure/function relationships, we present a plausible model for initial concentration and/or binding of the drug to Pgp.

References:

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